Special Congressional Funds for Type 1 Diabetes Research

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NIDDK Participation in Initiatives Supported, in Whole or in Part, by Special Funds Provided by the Congress Specifically For Type 1 Diabetes Research

In addition to initiatives, extensions and expansions to be funded through regularly appropriated funds, this Implementation Plan also contains descriptions of NIDDK participation in FY 2002 initiatives to be funded through special funds provided by the Congress specifically for type 1 diabetes research. The following is a brief description of this funding source and the planning process for identifying these initiatives.

Background

Special funding for type 1 diabetes research, in the amount of $150 million over five years, was initially provided by the Balanced Budget Act (BBA) of 1997, P.L. 105-33 (now Section 330B of the Public Health Service Act). This funding was increased in amount and extended in time by Section 931 of the Benefits Improvement and Protection Act of 2000, which was incorporated into the FY 2001 Consolidated Appropriations Act, P.L. 106-554. These funds have been provided as a supplement to funds the NIH receives for diabetes research through the regular appropriations process. The NIDDK has a leadership role in the planning process for the allocation of these funds. Shown below is the funding stream from the public laws that have provided these special funds to the Secretary.

Special Funds for Type 1 Diabetes Research—in Millions of Dollars

	FY98	*FY99*	*FY00*	*FY01*	*FY02*	*FY03*	*Total*
P.L. 105-33	*30.0*	*30.0*	*30.0*	*30.0*	*30.0*	-----	*150.0*
P.L. 106-554	-----	-----	-----	*70.0*	*70.0*	*100.0*	*240.0*
Total	*30.0*	*30.0*	*30.0*	*100.0*	*100.0*	*100.0*	*390.0*

Research Planning Process

To ensure the most scientifically productive use of the special funds, the NIDDK initiated a collaborative planning process that involves the participation of the relevant institutes and centers of the NIH, the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA), and the two major diabetes voluntary organizations: the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA). Critical to this process is scientific advice the NIH has garnered from a variety of scientific workshops and conferences, as well as the recommendations in the five-year plan of the congressionally established Diabetes Research Working Group.

Central to this process is the pursuit of six major research goals that offer exceptional promise for the treatment and prevention of type 1 diabetes, as outlined below:

I. Goal: To identify the genetic and environmental causes of Type 1 Diabetes
   A. Genetics of Type 1 Diabetes
   B. Epidemiology of Type 1 Diabetes
   C. Animal Models for Study of Genetics and Immune Mechanisms of Type 1 Diabetes
II. Goal: To Prevent or Reverse Type 1 Diabetes
III. Goal: Develop Cell Replacement Therapy
IV. Goal: Reduce or Prevent Hypoglycemia in Type 1 Diabetes
V. Goal: Prevent or Reduce the Complications of Type 1 Diabetes
VI. Goal: Attract New Talent to Research on Type 1 Diabetes

GOAL I. TO IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

POPULATION-BASED EPIDEMIOLOGY STUDY TO IDENTIFY GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

FY 2002 Action

An October workshop will bring together experts with a broad range of expertise relevant to the etiology of type 1 diabetes to provide advice to the NIDDK on potential longitudinal epidemiologic studies to identify environmental triggers that lead to the development of type 1 diabetes in patients with a genetic susceptibility and factors that impact on the autoimmune process leading to diabetes. Based on the recommendations obtained, a solicitation will be issued for creation of a cooperative group. It is anticipated that this effort will involve recruiting a large, cohort of newborns in whom long-term follow-up and comprehensive evaluations would take place.

Background

Type 1 diabetes is one of the most common and serious chronic diseases in children and appears to be increasing globally, particularly in the very young. The etiology of the disease, however, remains unclear. Epidemiologic patterns, including the higher incidence of type 1 diabetes in Caucasians compared with African Americans and Hispanics, an increased risk at puberty, and its more frequent onset during winter months, suggest that viruses, nutrition, and socioeconomic factors may contribute. Numerous studies have investigated environmental influences but have yielded conflicting results, in part perhaps due to a failure to account for genetic susceptibility, a failure to begin observation of individuals at very early ages, and the inability to follow a sufficient sample of individuals long-term on a frequent basis incorporating methods that can detect potential pathogens and other environmental influences.

Several studies are either ongoing or beginning in Colorado, central Florida, and the state of Washington, with the aim of establishing cohorts of newborns from the general population who are identified to be at genetic risk for type 1 diabetes. These cohorts are to be followed for the onset of various beta cell autoantibodies, with documentation of early childhood diet, reported infections, and vaccinations; certain case-control studies are planned to investigate selected potential environmental determinants. The power of the existing ongoing population-based studies could be enhanced through collaboration and expansion into a national network with standardized protocols, a coordinating center and central laboratories. The cooperative group should be sufficiently large to allow for analyses of gene-environmental interactions using both diabetes and islet autoimmunity as endpoints and include meaningful representation of the major racial/ethnic groups.

The experts attending the workshop will suggest optimal study populations and study designs. Presentations will focus on what we currently know about the initiation of islet autoimmunity and progression to type 1 diabetes, the role of specific environmental factors in the pathogenesis of type 1 diabetes, the ontogeny of islet tolerance and autoimmunity, and novel methods for investigating immunopathogenesis and beta cell function. The workshop will then lead to discussion of new studies that are needed and are feasible to conduct, how they may interact with ongoing studies, and finally to optimal study populations and study designs for these new studies.

Research Goals and Scope

This project is likely to establish a large, population-based cohort of newborns identified from the general population as genetically at risk for type 1 diabetes and to follow this cohort through the high risk age (e.g., 0 to 15 yrs) to identify additional genetic and environmental causes of diabetes. The project will probably involve a long-term cooperative group with multiple population-based clinical centers, a coordinating center, and central laboratories.

GOAL III. DEVELOP CELL REPLACEMENT THERAPY

COMPREHENSIVE PROGRAMS IN BETA CELL BIOLOGY (RFA DK-02-014)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-014.html

FY 2002 Action

The NIDDK is seeking to intensify investigator-initiated collaborative research aimed at understanding the signaling pathways in the adult pancreatic beta cell, and at elucidating how the different cell types of the pancreatic islet integrate these signaling networks. This initiative is intended to support large multi-component projects of outstanding investigators with innovative, high impact studies focused on the beta cell and the adult pancreatic islet; to attract established investigators who can bring novel or advanced techniques, tools and concepts from other areas of research to the study of beta cell biology; and to foster interdisciplinary approaches to the study of beta cell biology. Use of emerging genomic and proteomic methods to elucidate beta cell specific trafficking events, signaling pathways, and to determine novel components of the islet microenvironment required for proper beta cell function are encouraged. The ultimate goal is to use this increased understanding of the biology of the pancreatic islet to develop novel approaches to the treatment of diabetes. In further support of this initiative, the NIDDK will hold a workshop, "Beta Cell Biology in the 21st Century: Engineering a Pathway to Greater Understanding", on November 26-28, 2001. (http://www.betacellbiology.niddk.nih.gov).

Background

This RFA is a direct response to recommendations of the congressionally established Diabetes Research Working Group detailed in its report "Conquering Diabetes, A Strategic Plan for the 21st Century." One of the extraordinary research opportunities recommended by the plan was to better define signaling in the beta cell, and to use this increased knowledge of beta cell biology to develop novel treatments for diabetes. To this end, the NIDDK has initiated the "Comprehensive Beta Cell Project," which includes the "Functional Genomics of the Developing Endocrine Pancreas" project and the "Beta Cell Biology Consortium." Together these projects are designed to enumerate all the protein coding regions uniquely expressed in the developing and adult beta cells from human and mouse, to clone the associated mRNAs, and to gain a better understanding of beta cell development and differentiation in hopes of obtaining an unlimited supply of new beta cells or islets for use in long-term treatment of type 1 diabetes mellitus. The current initiative is designed to solicit research aimed at understanding the signaling pathways and signaling environment in the adult pancreatic beta cell, and at understanding how these signaling cascades are integrated in the pancreatic islet.

Research Goals and Scope

Much of the beta cell research reported to date has been carried out in cell lines derived from insulin-producing tumors (e.g., mouse and rat insulinomas), and in modified neuroendocrine cells (e.g., mouse AtT20 cells). These cell lines have proven very useful for *in vitro* studies of insulin secretion. However, these culture systems do not accurately recapitulate all of the normal physiology of the beta cell in the pancreas. Interaction of the various endocrine cell types of the islet with each other, and with their micro-environment, is critical to the proper functioning of the adult beta cell.

The current objective is to further our understanding of the many signaling cascades functioning in the pancreatic beta cell. To achieve this goal, the "Comprehensive Programs in Beta Cell Biology" RFA will support multidisciplinary investigator-initiated projects that explore numerous aspects of beta cell biology. Investigators applying to this RFA are encouraged to use genome-wide studies (genomics and proteomics), advanced imaging techniques, analytic methods, and state-of-the art cell biological approaches to investigate research opportunities in the beta cell such as:

- Elucidating which proteins are expressed specifically in the beta cell, as well as in the other endocrine cells of the adult pancreatic islet.
- Understanding the intra- and intercellular signaling pathways that lead to responses such as insulin secretion and amino acid transport.
- Elucidating the many signaling pathways initiated at the plasma membrane, and determining the molecules (proteins, lipids, small metabolites and ions) important for integration of these signals in the cytoplasm, and in the nucleus where complex cellular machinery regulates the transcription and translation of beta cell specific genes.
- Understanding the intra- and inter-cellular interactions between the different cell types of the pancreatic islet and the extracellular matrix, both in time and space, and elucidating how these signaling pathways may be different in healthy islets and in the dysfunctional islets resulting from the development of diabetes mellitus.

Presently, it will remain instructive to use established beta cell lines to characterize potential ligands and intracellular binding partners for newly discovered beta cell receptors, to identify potential substrates for beta cell specific enzymes, and to try to understand the complex signaling networks functioning in the beta cell. However, these new findings, as well as existing ideas about signaling pathways and cascades in the beta cell, will ultimately need to be studied in a more physiologically relevant milieu. This could include freshly isolated islets or improved beta cell models, as they become available, or islets produced *via* differentiation of progenitor cells. Likewise, use of gene inactivation and protein knock-in and knock-out experiments to study the role of newly identified beta cell proteins in whole animal physiology will be important.

GOAL III. DEVELOP CELL REPLACEMENT THERAPY

IMAGING PANCREATIC BETA CELL MASS, FUNCTION, ENGRAFTMENT OR INFLAMMATION (RFA DK-02-002)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-002.html

FY 2002 Action

A solicitation will be issued on "Imaging Pancreatic Beta Cell Mass, Function, or Inflammation" to further stimulate the development of techniques or reagents leading to the ability to image or otherwise non-invasively detect pancreatic islet beta cells *in vivo*, and measure their mass, function, or evidence of inflammation, or to monitor engraftment of transplanted isolated pancreatic islets. It is anticipated that research from funded projects will contribute to the eventual development of a clinical exam that can be used for monitoring disease progress and response to therapy in diabetics and in people strongly at risk for diabetes.

Background

Imaging technology has advanced rapidly in recent years, making it possible to image small or deep structures that have until now been impossible. It would be of great benefit to the diabetes community to be able to image the beta cells of the pancreatic islets. Through major histocompatibility complex (HLA) typing and measurement of certain antibodies, it is now possible to identify those individuals that are at risk for developing type 1 diabetes. Those at risk for type 2 diabetes can be identified through family history and measurements of insulin resistance. However, little is known about the natural history of beta cell mass, turnover and cell lifetime, or the course of inflammation in diabetes. This is principally because the pancreas is a highly heterogeneous organ that is difficult to biopsy, and beta cell mass is only 1 to 2 percent of the organ. Insulin secretory capacity can be measured, but it is a poor reflection of beta cell mass. Recent advances in imaging techniques make it likely that a clinical exam to monitor beta cell number, mass, function, or lymphocyte infiltration/inflammatory activity can soon be established. This would allow high-risk individuals to be monitored prior to onset of diabetes; patients could be monitored over the course of their disease to determine the exact stage of their disease; and it would also allow monitoring responses to therapy. To achieve these goals the NIDDK issued RFA DK-99-018; this is being reissued in the current initiative.

Type 1 diabetes is being successfully treated using pancreas transplantation, and researchers are now able to achieve insulin independence in patients by transplanting healthy, functioning isolated pancreatic islets into patients. In the course of evaluating this technique, it would be of great clinical benefit to be able to identify the location, number, viability, growth and function of these grafts, and to non-invasively monitor their response to immune modulating therapy using imaging.

Research Goals and Scope

The objective of this initiative is to support the development of imaging techniques and reagents that could be used to measure beta cell mass, function, or inflammation with the hope that these technologies can aid in diagnosis and treatment of diabetic and prediabetic patients in the clinic. Projects submitted to this initiative may describe research aimed at developing an imaging technique for this application, identifying

unique aspects of the beta cell or islet physiology or function that could be exploited for imaging, developing animal models to test imaging protocols, or developing new contrast agents that can be targeted specifically to the beta cell. In addition, projects to image immune cells, transplanted islets, or inflammation would be welcome.

GOAL III. DEVELOP CELL REPLACEMENT THERAPY

NON-HUMAN PRIMATE IMMUNE TOLERANCE COOPERATIVE STUDY GROUP (RFA AI-01-006)

http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-01-006.html

FY 2002 Action

This RFA solicits applications from single institutions and consortia of institutions to participate in the Non-Human Primate Immune Tolerance Cooperative Study Group (NHPCSG). The NHPCSG is a multi-center, cooperative research program focused on the study of immune tolerance in non-human primate models of kidney and islet allograft rejection, asthma and allergic diseases and autoimmune diseases. The goals of this research program are to: evaluate the safety and efficacy of novel tolerance induction regimens; elucidate the mechanisms of the induction, maintenance and loss of tolerance; and develop and validate biomarkers for induction, maintenance, and loss of tolerance in these immune-mediated disorders.

Background

Numerous panels convened by the NIH have made research on immune tolerance a high scientific priority. The Diabetes Research Working Group, charged with developing a strategic research plan for NIH-funded diabetes research. identified research on autoimmunity and the beta cell as one of five extraordinary opportunities and recommended expanded research on islet transplantation and immune intervention as well as support of centers using large animal models to test new therapies for type 1 diabetes. The National Institute of Allergy and Infectious Diseases (NIAID) Expert Panel for Research on Immune Tolerance, the NIAID Expert Panel on Ethical Issues in Clinical Trials of Transplant Tolerance and the Expert Review Panel for NIAID's Extramural Transplantation Research Program identified non-human primate tolerance research as an essential step to provide "...critical data on safety, toxicity and potential efficacy that cannot be obtained ethically in human clinical trials." In 1999, research on non-human primate models of kidney and islet transplantation was expanded though an RFA co-sponsored by NIAID, NIDDK and the National Center for Research Resources. The current RFA seeks to expand support for immune tolerance research in kidney and islet transplantation and initiate support for immune tolerance research in non-human primate models of other immune mediated diseases.

In this RFA, immune tolerance is defined as a lack of a pathogenic immune response to allogeneic, environmental, or self-antigens in the absence of ongoing immunosuppressive therapy. Tolerance may be induced by a variety of approaches, including clonal deletion, clonal anergy, immune deviation, or suppression. Projects should be designed to meet these goals in established and new non-human primate models of kidney and islet transplantation, asthma and allergic diseases, and autoimmune diseases. Because the ultimate purpose of this RFA is to develop candidate tolerogenic approaches for the treatment of immune-mediated diseases in humans, the sponsors expect that there will be reciprocal communication between the NHPCSG and the Immune Tolerance Network and Type 1 Diabetes TrialNet.

Research Goals and Scope

The purpose of this initiative is to support a multi-site cooperative research program to develop tolerance induction protocols in non-human primate models of immune-mediated diseases. For purposes of this RFA, immune tolerance is defined as a lack of a pathogenic immune response to allogeneic, environmental, or self-antigens in the absence of ongoing immunosuppressive therapy. Tolerance may be induced by a variety of approaches. All participating sites will use uniform controlled study designs and standardized data collection procedures. Specifically, the cooperative research program will design and conduct studies on: (1) the safety and efficacy of tolerance induction therapies alone, in combination with immunosuppressive therapies, and in combination with immunosuppressive therapy withdrawal; and (2) the underlying mechanisms of action of the therapeutic approaches being evaluated, including changes in immune response and function and measures of the induction, maintenance, and loss of donor-specific tolerance and also development, evaluation, and validation of biomarkers of immune tolerance.

This RFA will not provide support for studies in animal models other than non-human primates or improvement of the viability or supply of organs, tissues, or cells for transplantation or preliminary development of immune-mediated disease models in non-human primates or xenotransplantation into non-human primates. However, this RFA will provide support for costs associated with the procurement of allogeneic non-human primate islets and kidneys.

GOAL III. DEVELOP CELL REPLACEMENT THERAPY

GENE TRANSFER APPROACHES TO ENHANCE ISLET TRANSPLANTATION (RFA DK-02-020)

FY 2002 Action

This RFA will solicit applications to develop gene transfer approaches to enhance islet transplantation. The purpose of this RFA is to develop *ex vivo* gene transfer approaches to engineer beta cells or alter islets to enhance viability that could have advantages for transplantation. It is soliciting pilot and feasibility grants to explore gene transfer techniques that could be applied to enhanced islet transplantation.

Background

Type 1 diabetes is estimated to affect one million Americans—many of them children. These individuals must adhere to a regimen of life-long dietary restriction, glucose monitoring and insulin administration, and even the most vigorous effort is not sufficient to normalize glucose levels. Major mortality and morbidity are from the long-term complications of the disease including blindness, neuropathy, renal and cardiovascular disease. Recently, promising results have been achieved in a several patients with islet transplantation using a new combination of drugs that prevent rejection and halt autoimmune destruction of transplanted islets. While these results are promising, the major obstacle to the widespread application of this treatment is the limited supply of islet cells.

Research Goals and Scope

Novel approaches are needed to develop new sources of beta cells or islets for transplantation. Gene transfer approaches can be used to alter the properties of somatic cells. Recently, several new viral vectors, especially the lentiviral vectors, have shown promise for introducing genes into beta cells. One possible approach to this problem is to use gene transfer techniques to develop beta cells with new properties that would be useful for transplantation.

Since these are preliminary studies to explore the appropriate use of this new technology and to demonstrate its feasibility, the NIDDK is using the exploratory/developmental grant mechanism. These grants can be used to demonstrate the feasibility of an approach and to develop preliminary data for a future regular research grant submission. This mechanism allows investigators to test new approaches where there are limited preliminary data but a strong rationale and a reasonable expectation of feasibility. Some of the approaches that need to be explored are enumerated below. Relevant topics listed below are only examples and should not be construed as required or limiting.

- Investigate the use of growth promoting genes to derive beta cells or islets that can be expanded in culture while maintaining or reintroducing the differentiated phenotype for transplantation.
- Derive beta cells or islets from other tissues or progenitor cells by introducing genes needed to develop the differentiated beta cell phenotype.
- Engineer beta cells or islets that have enhanced resistance to immune destructive or apoptotic signals.
- Engineer beta cells or islets that elicit a reduced immune response.

GOAL IV. REDUCE OR PREVENT HYPOGLYCEMIA IN TYPE 1 DIABETES

UNDERSTANDING HYPOGLYCEMIA UNAWARENESS IN PATIENTS WITH DIABETES (RFA DK-01-031)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-031.html

FY 2002 Action

The NIDDK, in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research, the National Institute of Child Health and Human Development (NICHD), and the Juvenile Diabetes Research Foundation International (JDRF), has issued an RFA inviting applications to address the problem of hypoglycemia unawareness in patients with diabetes.

Background

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensified diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. However, with current treatment modalities, tight control remains an unattainable goal for many people with diabetes.

For many individuals with diabetes, episodes of severe hypoglycemia are the major obstacle to the achievement of euglycemia and the prevention of long-term complications. Hypoglycemia is frightening to patients and their families. Acutely, diminished brain function during a hypoglycemic episode poses potential physical danger to the patient. In addition, recurrent hypoglycemia may impose long-lasting damaging effects on the brain, resulting in impairment of memory or other cognitive functions. This is especially a concern in the early childhood years when the nervous system is still developing.

In addition to adversely affecting cognition, recurrent hypoglycemia also impairs the body's defense mechanisms against hypoglycemia, creating a vicious cycle for the patient. Normally, hypoglycemia triggers a series of hormonal and neural responses designed to restore glucose concentration towards normal to maintain brain metabolism. A component of this counterregulatory response is the secretion of epinephrine, which generates "neurogenic" symptoms (e.g., palpitations, sweating, anxiety) that serve to warn the patient of the dropping blood glucose. The patient can then take action (i.e., eat) to help reverse the hypoglycemia. However, a major problem in many individuals with diabetes is a progressive decay in the counterregulatory response over time. Falling blood glucose levels do not trigger epinephrine secretion and, therefore, no neurogenic symptoms occur to warn the patient of a problem. This results in "hypoglycemia unawareness" and can result in prolonged exposure to hypoglycemia, resulting in potential brain injury, seizure or loss of consciousness. The development of hypoglycemia unawareness makes the institution of intensified blood glucose control more difficult and puts patients at risk for severe hypoglycemia-related complications.

To highlight the problem of hypoglycemia in individuals with diabetes, the JDRF, the American Diabetes Association (ADA), NIDDK, NINDS, NICHD, and NASA

cosponsored a workshop on Hypoglycemia and the Brain on September 7-8, 2000. Participants in the workshop identified a number of knowledge gaps requiring future research. This RFA is a first step to address the critical problem of hypoglycemia unawareness in diabetes.

Research Goals and Scope

This RFA solicits basic and clinical studies to: (1) define the mechanisms underlying the loss of hypoglycemia awareness in patients with diabetes; and (2) develop novel approaches to prevent or reverse hypoglycemia unawareness. Recent scientific advances (e.g., the advent of new information regarding neurohumoral factors involved in energy metabolism, the development of new imaging technologies, and the availability of continuous glucose monitoring) potentially open up new avenues of exploration. Appropriate topics for investigation under this RFA would include but are not limited to:

- Studies to elucidate the identity, location, and functional characteristics of glucose-sensing neurons, and determine whether these characteristics are altered by recurrent episodes of hypoglycemia.
- Studies to identify the neuronal populations involved in generating hypoglycemic awareness, and the potential effects of recurrent hypoglycemia upon these neural systems.
- Studies to identify the neuroendocrine or biochemical signals generated by hypoglycemia, and the changes in these signals over recurrent episodes of hypoglycemia.
- Studies to measure altered neuronal activation, blood flow or other physiological indices in the brain in response to recurrent hypoglycemia and in the setting of hypoglycemia unawareness.
- Studies to understand the relative roles and interactions of peripheral and central glucose sensing, and determine whether/how these are altered with recurrent hypoglycemia or when hypoglycemia unawareness develops.
- Studies to define the interaction of central and autonomic neural systems with endocrine and metabolic signals (including neurohumoral factors), and determine whether/how these signals are disrupted by recurrent hypoglycemia.
- Studies to determine whether altered glucose transport may play a role in hypoglycemia unawareness.
- Studies to explore the effect of sleep on counterregulatory responses, and to determine the role of nighttime hypoglycemia in loss of awareness.
- Studies to determine whether there are changes in counterregulatory mechanisms with age, and whether *in utero* exposure to acute or recurrent hypoglycemia influences postnatal hypoglycemia awareness.
- Studies to assess the role of brain glycogen in supporting brain metabolism during hypoglycemia, and its possible role in the development of hypoglycemia unawareness.
- Studies to assess the extent to which uncontrolled hyperglycemia may impair neuronal function and contribute to hypoglycemia unawareness.
- Studies to determine whether different treatment regimens for diabetes affect counterregulatory mechanisms.
- Studies to develop and test strategies for promoting glucose sensing by the brain.
- Studies to develop and test strategies to restore counterregulatory responses in patients with hypoglycemia unawareness.

GOAL IV. REDUCE OR PREVENT HYPOGLYCEMIA IN TYPE 1 DIABETES

EFFECTS OF HYPOGLYCEMIA ON NEURONAL AND GLIAL CELL FUNCTION (RFA NS-02-008)

http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-02-008.html

FY 2002 Action

This RFA solicits applications for studies designed to elucidate the effects of acute and recurrent episodes of hypoglycemia on glial and neuronal cells of the developing and mature central nervous system.

Background

Large-scale clinical trials have established the importance of intensified diabetes control in reducing the complications that result from poorly controlled hyperglycemic levels. However, therapeutic efforts to closely regulate glycemic levels may occasionally cause inadvertent and recurrent episodes of severe hypoglycemia. Acute hypoglycemic episodes may result in transient or persistent alteration of brain function. When plasma glucose levels fall below 3 mmol/L, cortical function deteriorates; confusion, abnormal behavior, seizures and coma can result. The effects of acute or recurrent episodes of hypoglycemia on the cells of the central nervous system are potentially harmful and may impose long-lasting damaging effects on the brain. This is of particular concern in the early childhood years when the nervous system is still developing and in fetuses exposed to maternal hypoglycemia.

The regulation of cerebral metabolism in settings of altered glycemia is poorly understood. It is recognized that astrocytes can provide fuel substrates to neurons, and that the glial cells contain glycogen. However, the regulation of glial intracellular glycogen and patterns of glycogen breakdown in settings of varied glycemic states is unknown. In the context of altered glycemic levels, alternative fuel sources supplied by astrocytes could ameliorate the effects of hypoglycemia on other cells of the central nervous system. However, recurrent hypoglycemic insults could potentially affect the ability of astrocytes to provide alternative fuel substrates, and this is an area that warrants investigation. In addition, the regulation of endothelial cell expression of glucose transporters may change in response to varied glycemic levels.

There is substantial evidence that hypoglycemia alters human behavior, and recurrent episodes of severe hypoglycemia may lead to memory loss or impaired cognitive function. The pathogenesis of hypoglycemic-induced nerve cell injury is largely unknown; mechanisms that could result in damage to cells of the CNS include, but are not limited to, excitotoxicity related to a dysregulation of the glutamate-glutamine cycle or an impaired capacity of astrocytes to generate reducing equivalents in the presence of oxidative stress. To understand the effects of acute or recurrent hypoglycemia on the cells of the central nervous system, it is essential to characterize the response of CNS cells to reduced glycemic levels, to determine the extent of CNS cell injury induced by hypoglycemia, and to identify the mechanisms involved in hypoglycemia-induced cell or tissue damage in brain.

To highlight the problem of hypoglycemia in individuals with diabetes, the Juvenile Diabetes Research Foundation International, the American Diabetes Association, NIDDK, the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, and NASA co-sponsored a workshop on Hypoglycemia and the Brain on September 7-8, 2000. Participants in the workshop identified a number of knowledge gaps requiring future research which will be addressed in this and complementary RFAs.

Research Goals and Scope

This RFA solicits basic studies to: (1) define the effect of varying glycemic levels on cerebral metabolism, transport of glucose across the blood brain barrier, and astrocytic regulation of substrates for neuronal metabolism; and (2) determine the pathological consequences of acute and recurrent hypoglycemic insult on cells of the central nervous system. While an ischemic insult in the CNS subjects neurons and glia to glucose deprivation coupled with hypoxia, a hypoglycemic insult exposes the cells of the CNS to glucose deprivation in a normally oxygenated environment. The state of tissue oxygenation directly impacts the ability of cells to maintain glycolysis. Thus, this RFA seeks to solicit studies aimed at examining the effects of glucose reduction, which is physiologically relevant under normoxic conditions.

GOAL IV. REDUCE OR PREVENT HYPOGLYCEMIA IN TYPE 1 DIABETES

NEW APPROACHES TO PREVENT HYPOGLYCEMIA IN PATIENTS WITH DIABETES (RFA DK-01-032)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-032.html

FY 2002 Action

The NIDDK, in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research, the National Institute of Child Health and Human Development (NICHD), and the Juvenile Diabetes Research Foundation International (JDRF), has issued an RFA to solicit applications for clinical studies designed to enhance understanding and prevention of hypoglycemia in patients with diabetes.

Background

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensified diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. However, with current treatment modalities, tight control remains an unattainable goal for many people with diabetes. For example, in the DCCT, fewer than five percent of individuals receiving intensified treatment maintained normal hemoglobin A1c levels.

To achieve glycemic control, many patients must walk a tightrope, balancing euglycemia against the danger of low blood glucose. Indeed, for many individuals with diabetes, episodes of severe hypoglycemia are the major obstacle to the achievement of euglycemia and the prevention of long-term complications. Hypoglycemia is frightening to patients and their families. In fact, for some individuals or their families, fear of hypoglycemia may outweigh concern over long-term complications of diabetes, leading to inadequate glycemic control. Fear of hypoglycemia is well-founded, as low blood glucose levels impart significant morbidity and mortality. Two to four per cent of deaths among individuals with type 1 diabetes have been attributed to hypoglycemia. Acutely, diminished brain function during a hypoglycemic episode poses potential physical danger to the patient. In addition, recurrent hypoglycemia may impose long-lasting damaging effects on the brain, resulting in impairment of memory or other cognitive functions. This is especially a concern in the early childhood years when the nervous system is still developing.

Recurrent hypoglycemia may also impair the body's defense mechanisms against hypoglycemia, creating a vicious cycle for the patient. A major problem in many individuals with diabetes is a progressive decay in the counterregulatory response over time, resulting in "hypoglycemia unawareness." The individual fails to become aware of hypoglycemia and does not initiate appropriate responses. This can result in prolonged hypoglycemia, with consequent brain injury, seizure or loss of consciousness. Children and the elderly may be particularly vulnerable to the development of hypoglycemia and to its deleterious effects. Young children cannot reliably report or interpret symptoms of hypoglycemia. In older individuals, decline of beta adrenergic function with age, coupled with other medical problems (e.g., mild renal impairment which could alter drug

metabolism), may predispose to the risk of hypoglycemia and hypoglycemia unawareness. Unrecognized hypoglycemia could contribute to subtle declines in mental function that might simply be attributed to "dementia."

Hypoglycemia occurs because of a mismatch between insulin dose, food intake and energy expenditure. Despite vigilant blood sugar monitoring and adherence to treatment regimens, euglycemia often cannot be achieved safely (i.e., without the occurrence of hypoglycemia), because current treatment modalities do not mimic normal, physiologically regulated insulin secretion.

To address this critical problem in diabetes, the JDRF, the American Diabetes Association (ADA), NIDDK, NINDS, NICHD and NASA cosponsored a workshop on Hypoglycemia and the Brain on September 7-8, 2000. Participants in the workshop identified a number of knowledge gaps requiring future research. This RFA is a first step toward addressing the problem of hypoglycemia in diabetes.

Research Goals and Scope

This RFA solicits clinical studies to: (1) define the scope and nature of hypoglycemia in individuals with diabetes; and (2) develop and test strategies to prevent the development of hypoglycemia in patients with diabetes, or to ameliorate its effects. Recent scientific advances, including the availability of continuous glucose monitoring, potentially open up new avenues of exploration. Appropriate topics for investigation under this RFA would include but are not limited to:

- Studies to determine the prevalence of hypoglycemia in patients with diabetes, with a focus on delineating differences among various age groups (e.g., children, adults, the elderly).
- Studies to delineate the role of age, gender, race/ethnicity, socioeconomic status and other factors in the risk of hypoglycemia.
- Studies to identify factors, including method of treatment, exercise, nutrition, or duration of diabetes, which affect risk of hypoglycemia.
- Studies to establish normative data for blood glucose levels, particularly in children, throughout a 24-hour period.
- Studies to determine whether there are changes in mechanisms with age.
- Studies to determine whether intensive glucose control during pregnancy has adverse effects on the developing fetus.
- Studies to determine whether alternative fuels (e.g., ketones) can provide a buffer against hypoglycemia.
- Studies to assess the reliability and utility of continuous glucose sensors in detecting falling blood glucose levels and in preventing severe hypoglycemia.
- Studies to determine whether the occurrence of hypoglycemia can be minimized by altering the timing of drug delivery or by drugs with altered kinetics.
- Studies to determine whether different treatment regimens for diabetes affect mechanisms.
- Studies to evaluate whether there are differences in counter regulation between individuals with type 1 and type 2 diabetes.
- Studies to develop and test strategies for minimizing the risk of hypoglycemia with intensive glucose management.

GOAL V. PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

SURROGATE ENDPOINTS FOR DIABETIC MICROVASCULAR COMPLICATIONS (RFA DK-02-016)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-016.html

FY 2002 Action

The NIDDK, in collaboration with the National Eye Institute and the National Institute of Neurological Disorders and Stroke, will issue an RFA to solicit applications to develop and validate biomarkers for the microvascular complications of diabetes.

Background

Prevention and treatment of long-term complications remain critical problems in the management of type 1 and type 2 diabetes mellitus. In the U.S., diabetes is the leading cause of new blindness in working-age adults, of new cases of end-stage renal disease and of non-traumatic lower leg amputations. Diabetes has been estimated to cost the U.S. economy over $98 billion annually; much of this cost is related to the treatment of the long-term micro- and macrovascular complications of diabetes. Identification of patients at risk for the development of complications, with the hope of early intervention, is a public health priority. Early intervention is essential, because, by the time symptoms of disease are recognized, irreparable structural organ damage may have already occurred.

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the U.S., accounting for over 40 percent of cases. Major risk factors for the development of diabetic nephropathy include duration of diabetes and poor metabolic control. However, there is considerable ethnic/racial variability in the incidence of nephropathy, and not all patients with prolonged hyperglycemia develop ESRD, suggesting a strong genetic component to susceptibility. Microalbuminuria is the best available non-invasive predictor of diabetic nephropathy risk; however, the predictive value of microalbuminuria for the progression to overt nephropathy is not precise. Thus, it might be desirable to intervene in patients with normal albumin excretion, if patients at high risk for the development of nephropathy could be identified.

Neuropathy is a frequent complication of diabetes. However, symptoms may not occur until after neurological damage has occurred. Currently available methods for assessing nerve function either lack reliability (nerve conduction studies) or are invasive (sural nerve biopsy). Diabetic neuropathy is often associated with peripheral vascular disease and impaired wound healing, resulting in more than 200,000 cases of foot ulcers and 80,000 amputations per year. Thus, a top priority is the development of simple and reliable biomarkers of early damage, to allow effective early intervention (i.e., before symptoms develop) to prevent ulcerations and disability. In addition, there are currently no widely accepted non-invasive surrogate endpoints that can be used for clinical trials.

Diabetes is the most common cause of new cases of blindness among working age adults. As with other microvascular complications, risk is related to duration of diabetes and glycemic control. By the time visual acuity is affected, significant retinal damage has already occurred. Fluorescein angiography and fundus photography are effective methods for detecting retinopathy; however, these techniques can only be used to detect

disease in its late stages, when some permanent visual loss has already occurred. Biomarkers are, therefore, needed for determining risk for retinopathy and for detecting disease at its earliest stages, so that more effective interventions can be used to prevent visual loss. In addition, because these techniques detect only late stages of retinopathy, trials of prevention or treatment regimens require long follow-up to detect clinically significant differences. Markers of early disease could potentially shorten the duration of clinical trials by allowing more sensitive detection of retinopathy progression.

Research Goals and Scope

This RFA invites basic and clinical research applications to develop biochemical, cellular, physiologic and genetic surrogate endpoints that can be used to predict risk, aid in early diagnosis and assess progression of the microvascular complications of diabetes. The overall goal of this RFA is to develop biomarkers that could be used as diagnostic tools for the individual patient, or as outcome measures to be used in clinical trials testing new therapeutic agents.

Recent studies of the pathogenesis of diabetic microvascular complications may provide clues for potential biomarkers of disease. For example, several growth factors have been implicated in the development of nephropathy, and some studies indicate that urinary excretion of TGF-beta may be an early marker of nephropathy. In addition, recent advances in molecular biology may open up new avenues of exploration for the development of surrogate endpoints. Thus, the use of gene or protein microarrays could provide powerful tools to screen for novel biochemical, cellular or genetic markers associated with disease susceptibility or progression. New advances in imaging technologies also may provide opportunities to detect microvascular abnormalities non-invasively and develop physiologic markers that are associated with diabetic complications. Appropriate topics for investigation under this RFA would include but are not limited to:

- Studies to identify and validate new biomarkers of early signs (i.e., before the onset of symptoms) of retinopathy, nephropathy or neuropathy.
- Studies to identify and validate new biomarkers that identify patients at risk for the development of retinopathy, nephropathy or neuropathy.
- Studies to identify and validate new diagnostic tools that can be used to monitor more sensitively the progression of retinopathy, nephropathy or neuropathy.
- Studies to identify biomarkers that could be useful in predicting susceptibility to or development of multiple microvascular complications (e.g., retinopathy and nephropathy).
- Studies to develop non-invasive measures of oxygenation or blood flow in relevant tissues (e.g., retina).

GOAL V. PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

IMAGING PERFUSION, OXYGENATION AND ANGIOGENESIS IN THE PERIPHERAL MICROCIRCULATION

FY 2002 Action

This initiative is a call for studies designed to apply imaging techniques that measure perfusion or tissue oxygenation at the level of the microvasculature to the study of diabetes and its complications. Very early detection of defective perfusion may help to identify those patients that are at risk for the microvascular complications of diabetes such as neuropathy that can lead to loss of sensation and the development of wounds in the hands and feet. Once identified, these patients can be specially flagged for intensive treatment in hopes of preventing complications. Also of interest is imaging inflammation and angiogenesis in peripheral tissues in order to monitor wound development and wound healing in diabetes, and identifying patients with severe tissue destruction that would benefit from revascularization procedures. The ultimate goal of this initiative is to provide the diabetes clinical community with reliable, inexpensive tools to detect the early stages of microvascular complications, identify patients likely to benefit from therapeutic interventions, and monitor disease progression and response to therapy.

Background

The Diabetes Control and Complications Trial (DCCT) for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes demonstrated that intensive control of blood glucose levels could dramatically reduce the devastating microvascular complications of diabetes. The UKPDS also demonstrated a benefit of rigorous blood pressure control in preventing microvascular complications. In the DCCT, development of complications was reduced both in patients without discernable microvascular damage and in those with evidence of early retinopathy at the start of the study. Thus patients identified at an early stage in the development of microvascular disease would have a special incentive to maintain good control of their blood glucose in an attempt to avoid future health problems. It may be possible to use modern imaging technologies, coupled with exercise or a vasoactive compound such as nitric oxide, to identify and localize parameters that correlate with an increased risk for developing microvascular diabetic complications. Candidate parameters might be blood flow, water diffusion, myoglobin or hemoglobin oxygenation, cytochrome oxidation state, or altered contrast agent extravascularization. Patients with established microvascular disease are at increased risk of foot ulceration that may progress and lead to amputation. It is often difficult to assess the extent of a lesion and patients with what appear to be superficial ulcers may benefit from the ability to locate and visualize the extent of inflammation to determine the optimal therapeutic approach. The ability to monitor blood flow or angiogenesis may also allow doctors to document early responses to therapy for wound healing. Angiography with contrast agents is associated with risks, particularly for patients with diabetic nephropathy. A non-invasive method of assessing circulation in the limbs of diabetic patients is needed that could identify candidates for revascularization surgery. Any of these phenomena may furthermore serve as surrogate markers in future clinical trials of prevention or treatment of microvascular complications, or may aid basic research to understand the pathogenesis of neuropathy. The ideal technologies would be fairly easy to implement, require relatively little training

of clinic personnel, and be inexpensive or employ already widely distributed medical equipment.

A variety of new spectroscopic and imaging technologies could provide direct and indirect measures of blood flow and tissue oxygenation with fine spatial resolution. MRI, optical, and ultrasound can be used to measure blood flow and blood volume. In the brain, oxyhemoglobin serves as an MRI contrast agent that is sensitive to neural activation. Other measurements of tissue oxygenation have been provided by optical spectroscopy of the oxidation states of cytochromes, hemoglobin and myoglobin. New methodologies, such as optical tomography, make the optical imaging of deep tissues possible. MRI is also used to measure the diffusion of water through tissue. In normal muscle and neural tissue, diffusion is constrained by the muscle fibers and nerve sheath. Disruptions in these structures due to underperfusion and hypoxia, or due to other types of damage secondary to diabetes may be detectable using MRI. The behavior of injected contrast agents may allow the detection of pathological microvessel characteristics such as leakiness, loss of patency, or obstruction.

A distinct but similar methodology, molecular imaging, uses contrast agents bound to antibodies or other targeting molecules that "light up" specific cell types or sub-organ structures. By exploiting the unique surface molecules expressed in growing vascular tissue and in cells of the immune system, molecular imaging has been successfully used to non-invasively visualize angiogenesis and inflammation. This might be valuable for monitoring wound healing, adequacy of debridment, and the extent of tissue involvement in patients with diabetic foot disease.

Research Goals and Scope

This RFA is intended to determine if measurements of tissue perfusion and oxygenation correlate with the severity of diabetic complications and/or predict susceptibility to complications, support the development of equipment specifically for use in the clinic, and support limited clinical trials to test the utility of potential methodologies for monitoring microvascular disease in the diabetic population. Collaborations between scientists with expertise in imaging and those with expertise in diabetic complications, or with animal models of diabetes, are encouraged. Appropriate topics for investigation under this RFA include but are not limited to: quantitatively image blood flow or tissue oxygenation in appropriate peripheral tissues during rest and mild exercise or pharmacological challenge, and determine if these parameters are altered in diabetes and its complications; evaluate diffusion, non-toxic contrast agent kinetics, etc. as markers for very early microvascular disease; find markers of very early nerve damage in peripheral tissues; image areas of infection and monitor the growth of new blood vessels during therapy for injuries related to diabetic complications; and develop machines (inexpensive, robust, portable) for imaging blood flow, oxygenation, etc. for the management of diabetes in the clinic or hospital environment. This RFA would also fund small clinical trials designed to apply imaging technology to measure perfusion, diffusion, oxygenation, angiogenesis, or inflammation in the diabetic population.

GOAL V. PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

PILOT AND FEASIBILITY PROJECTS TO PREVENT OR SLOW PROGRESSION OF DIABETIC NEPHROPATHY

FY 2002 Action

The purpose of this initiative is to identify interventions with the potential either to prevent diabetic nephropathy or slow its progression, and obtain sufficient preliminary data on their use to permit design of large-scale interventional trials.

Background

Patients with type 1 diabetes have approximately a 20 to 40 percent lifetime risk of developing renal failure. Renal disease incidence peaks 15 to 20 years after the onset of diabetes, when patients are in mid adulthood. After clinical recognition of the kidney complication, it typically progresses rapidly to renal failure over a period of three to five years. Patients with renal disease also tend to have disproportionate prevalence of cardiovascular complications. As a consequence, the lifetime burden of chronic renal failure is especially severe for patients with type 1 diabetes. Low levels of albumin excretion in the urine (microalbuminuria) are established as a strong risk factor/predictor for later development of overt diabetic nephropathy. Overt proteinuria (dipstick positive) is the next manifestation of the diabetic nephropathy and usually precedes notable reductions in glomerular filtration rate. Since patients with type 1 diabetes are typically under medical care during the two to three decades prior to development of renal failure, strategies to prevent the disease could potentially be implemented. The best current treatment for established diabetic nephropathy is use of converting enzyme inhibitors (CEIs), which do slow the progression of disease. However, their use to prevent the development of early disease is also being examined in clinical trials. To date, the available early data have not provided convincing evidence that they are useful preventive agents, although this important issue needs further study. Good blood pressure control and good glycemic control are also critical aspects of disease prevention. Nonetheless, many patients develop progressive disease in spite of adequate management of these factors, and new strategies, both to prevent disease and to slow its progression, are needed urgently.

Clinical trials to establish definitively that drugs either prevent diabetic kidney disease or slow its progression need to be long in duration and enroll large number of subjects. However, reduction in urine albumin excretion appears to be a useful surrogate marker in trials of therapies for established disease Thus, reductions in albumin excretion may help predict whether an intervention will protect patients from progressive renal insufficiency.

Research Goals and Scope

It is proposed to invite applications for pilot and feasibility studies to test new strategies for prevention and treatment of this disease. The request for applications will urge use of urine protein measurements, either albumin or total protein, as a surrogate marker for disease progression. It is assumed that, unless contraindicated, proteinuric subjects in the control and trial groups will be treated with CEI's at routine doses as the current standard of care, and that the studies would examine either addition of alternate agents or incremental effects CEI’s. Both interventions directed at further blockade of the renin-

angiotensin axis and manipulation of other pathways will be invited. Enrollment strategies should be developed to emphasize a patient population in young to mid adulthood and strong representation of patients with type 1 diabetes. If indicated, assessment of the impact of the intervention on retinopathy or neuropathy could be incorporated into the trial design.

GOAL VI. ATTRACT NEW TALENT TO RESEARCH ON TYPE 1 DIABETES

BENCH TO BEDSIDE RESEARCH ON TYPE 1 DIABETES AND ITS COMPLICATIONS (RFA DK-02-022)

FY 2002 Action
This Request for Applications (RFA) solicits research partnerships between clinical and basic biomedical researchers with the goal of translating advances in our understanding of the molecular basis of type 1 diabetes and its complications into new therapies for prevention, treatment and cure of this disease.

In these "bench to bedside" research partnerships, a team of clinical and basic scientists will conduct collaborative research that, if successful, will bring basic research advances from the laboratory to a point where a potential new therapy can be tested in patients or in preclinical studies in animal models.

Background
Type 1 diabetes is an autoimmune disease characterized by the destruction of the insulin-secreting beta cells of the pancreas by cytotoxic T cells. Diabetes is difficult to control with the current therapies available, and as a result patients with type 1 diabetes may suffer devastating consequences including accelerated cardiovascular disease, nephropathy, retinopathy, neuropathy, oral diseases and premature death. The incidence of type 1 diabetes appears to be increasing worldwide. Although the disease may occur at any age, the onset of type 1 diabetes peaks prior to twenty years of age. In some populations, about one percent of all newborns will develop type 1 diabetes during their lifetime.

Recent advances in fundamental science and in our understanding of the pathophysiology underlying type 1 diabetes and its complications offer tremendous promise for the development of new therapies. However, to reach this potential a number of obstacles must be overcome. These include inadequate animal models in which to test new therapies and lack of measures to predict or assess response to therapy in early trials of potential therapies. Most recently the success of islet transplantation in freeing individuals with type 1 diabetes from the need for insulin therapy has yielded great excitement and a new impetus for research to develop methods to attain an unlimited source of islets for transplantation and to minimize the toxicity of immunotherapy required for transplantation. Multi-disciplinary teams of basic and clinical scientists will be required to overcome these obstacles and hasten our ability to bring new approaches to therapy forward to be tested in clinical trials.

Research Goals and Scope
The overall objective of this RFA is to stimulate translational diabetes research by encouraging the formation of collaborative research teams composed of basic and clinical scientists focused on specific projects that have the potential to develop new therapies for type 1 diabetes or its complications. Applications must involve a team of clinical and basic scientists from a single or multiple institutions. It is expected that the combined expertise of the investigators will foster the development of a basic research finding to the point where the underlying hypothesis can be tested in a clinical trial or an animal

model to assess its value in the treatment and/or prevention of type 1 diabetes or its complications.

GOAL VI. ATTRACT NEW TALENT TO RESEARCH ON TYPE 1 DIABETES

INNOVATIVE PARTNERSHIPS IN TYPE 1 DIABETES RESEARCH (RFA DK-02-023)

FY 2002 Action
This Request for Applications (RFA) solicits research supporting collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and researchers from other research areas with expertise relevant to type 1 diabetes research.

Background
Type 1 diabetes is an autoimmune disease characterized by the destruction of the insulin-secreting beta cells of the pancreas by cytotoxic T cells. The incidence of type 1 diabetes appears to be increasing worldwide. Although the disease may occur at any age, the onset of type 1 diabetes peaks prior to twenty years of age. In some populations, about one percent of all newborns will develop type 1 diabetes during their lifetime. Those affected with type 1 diabetes suffer from devastating complications including accelerated onset of cardiovascular disease, neuropathy, nephropathy, retinopathy and premature mortality.

Research Goals and Scope
The objectives of this RFA are to attract new research talent to type 1 diabetes research, strengthen the ongoing efforts of type 1 diabetes researchers by providing access to specialized expertise or technologies relevant to their research, and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. Established type 1 diabetes researchers are encouraged to act as "talent scouts" and to actively identify and recruit leading scientists with relevant scientific expertise to the field of type 1 diabetes research.

Applications should propose collaborative research partnerships between independent principal investigators—one currently pursuing research relevant to type 1 diabetes and one (or more) with expertise relevant to some aspect of type 1 diabetes, which is not currently being applied by the investigator to research on this disease. Although it is not a requirement that the research partner(s) being recruited to diabetes research should never have worked on a project relevant to diabetes or its complications, diabetes related research should not have been a significant focus of his/her research effort. Review criteria will include consideration of whether one partner is new to diabetes research and is likely to make substantial contributions to the diabetes research effort. Each of the research partners should be a successful independent investigator with a track record of successful research accomplishments.